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Supplement

Familial occurrence of *Helicobacter pylori* infections

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Summary

Background: *Helicobacter pylori (Hp) is one of the most common human pathogens. There is no consensus concerning the incidence of Hp infections in siblings of the children infected with this pathogen. The reports concerning this problem are scarce, reporting incidences in siblings ranging from 37% to even 82%. The aim of the study was to assess incidence of Hp infections in siblings of the children with gastritis and/or duodenitis coincident with the infection.*

Material/Methods: *The study was carried out in a group of 60 children aged 3–18 coming from 39 families. Anamnesis concerning dyspeptic symptoms was collected and urea breath test (UBT) performed in order to detect Helicobacter pylori infection.*

Results: *Positive UBT results, indicating Hp infections, were obtained in 38 children (63.3%). The prevalence of infection was not age-related: in the group below 7 years of age infections were found in 75% of cases, in the group aged 7–15 years in 55.5%, and over 15 years of age in 66.7%. Fourteen children (23.3%) reported dyspeptic symptoms. In 12 of them (85.7%), Hp infection was diagnosed. Dyspeptic symptoms were significantly more frequent in children over 10 years of age (31.7%) than in those below 10 (5.3%).*

Conclusions: *1) The incidence of Helicobacter pylori infections in siblings of children with gastritis and/or duodenitis coincident with Hp infection is high. 2) High incidence of infections is observed even among the youngest children (3–7 years), but they are usually not accompanied by dyspeptic symptoms. 3) Dyspeptic symptoms, which may indicate peptic ulcer disease or gastritis in siblings of Hp-infected children are frequent and exacerbate over 10 years of age.*

Key words: *Helicobacter pylori* infection • UBT • family • siblings

BACKGROUND

According to current state of knowledge, *Helicobacter pylori* (Hp) is one of the most common human pathogens. About 50 % of human population is estimated to be infected [1]. The incidence of Hp infections ranges from 20 % to 90 % depending on development level of the country. It is most common in the countries with low socioeconomic status and high population density [2–4]. In all populations the incidence increases with age, and the age of contracting the infection is dependent on the living standards. Currently the infection is observed very rarely among children living in developed countries, whereas in the so-called Third World countries most children are infected. Similarly as in case of poliomyelitis and hepatitis A, the spread of infection is favored by low living standards, staying in large groups of children, numerous families living together on a small area, infected parents, sleeping in the same bed with other family members [4,5]. Surveys carried out in developed countries indicate that the incidence of Hp infections does not exceed 6–8 % among children below 10 years of age, and 12–15% among teenagers [3,6–10]. In developing countries 30–40% of children below 5 are already infected, whereas the incidence among teenagers reaches 70–80% [3,4, 11,12]. The annual rate of infection spread among children is 0.5–1% in developed countries, but 2–5 % in the developing ones [according to 5]. In Polish medical literature, the data concerning the incidence of Hp infections are not very abundant and usually concern the adult population. Most reports concerning children describe patients seeking medical assistance because of abdominal symptoms. The incidence of Hp infections among children is 30–40% and reaches 50 % among teenagers [13–16]. In the region of Łódź, Hp is detected in 15% of examined children below 2 years of age, ca. 25% of 3–5-year-olds, 28% of 6–10-year-olds and 45% of examined teenagers [17]. Przybyszewska [18], who examined children below 4 years of age in Cracow, observed Hp infections in 13% of cases. The above data indicate that the incidence of infections is, like in other countries of the world, growing with age and that in Poland, as well as

other countries of Central and Eastern Europe, it is very high, approximating the values observed in the so-called Third World rather than those reported in developed countries [19]. In view of high prevalence of Hp infections, as well as the fact that humans are the reservoir of the bacteria and the next of kin are usually the source of infections contracted in childhood, familial screening becomes particularly important in pediatrics. There is no consensus concerning the incidence of Hp infections in siblings of the children infected with this pathogen. The reports concerning this problem are scarce, reporting incidences in siblings ranging from 37% to even 82%. This is probably due to low reliability of serological test results in children [20–23].

Aim of the study

The aim of the study was to assess incidence of Hp infections in siblings of the children infected with the pathogen, as well as the influence of socioeconomic factors and Hp strain type isolated from the child (cagA+, cagA-) on the incidence of Hp infections among the next of kin.

MATERIAL AND METHODS

The first phase of the study involved random selection from among the patients of the Endoscopy Laboratory at the Gdańsk Medical University Department of Pediatrics, Gastroenterology and Oncology of a group consisting of 39 children with Hp infectios diagnosed on endoscopy by urease test. In all the children, the diagnosis was verified by PCR, which also allowed identification of the Hp strain responsible (cagA+, cagA-).

During the second phase, the siblings of the aforementioned 39 patients were examined. The prerequisite for qualification was living together with the patient. All the examined subjects completed, in the presence of a physician, a questionnaire containing data concerning dyspeptic symptoms, any diagnostic procedures performed for this reason in the past, living conditions and education level of parents. Then urea breath test was performed to detect Hp.

Thirty sisters and thirty brothers aged 3–18 (mean age 13.7±4.1) of the previously diagnosed children were examined.

^{13}C-Urea Breath Test, (^{13}C-UBT) is a noninvasive, completely safe diagnostic method allowing to detect the ongoing Hp infection. The method takes advantage of the extremely high urease activity of Hp and owing to the use of ^{13}C– a stable, non-radioactive, safe carbon isotope enables to detect Hp by determination of $^{13}CO_2$ concentration in the air expired by the patient according to the following reaction: $(NH_2)_2{}^{13}CO + H_2O \rightarrow {}^{13}CO_2 + 2\ NH_3$

The tests were carried out in the Endoscopy Laboratory at the Gdańsk Medical University Department of Pediatrics, Gastroenterology and Oncology. Within a few days, the expired air samples were sent to the Laboratory of Isotopes, Department of Clinical Physiology, Jagiellonian University College of Medicine, Cracow (Head: Dr W. Bielański), where they were analysed by spectrometry in infrared: the $^{13}CO_2/^{12}CO_2$ ratio was determined in the individual portions of expired air. The final result of the test was expressed as an increase of $^{13}CO_2/^{12}CO_2$ value in expired air portion after swallowing the capsule in comparison with samples collected at the baseline. An increase by 2.5% (*delta over baseline*) was regarded as a positive result. Comparison with baseline values is necessary because of the presence of trace amounts of ^{13}C isotope in the diet (products of plant origin, especially corn).

Statistical analysis

The frequency of individual characteristics of the studied population was compared using Pearson's test. If the population in a particular group was smaller than 10, Yates' modification of Pearson's test was used. The differences were considered statistically significant at significance level lower than 0.05 ($p<0,05$). The calculations were carried out using the STATISTICA for Windows software package, version 5.0 (StatSoft, Inc, USA).

RESULTS

The presence of cagA gene encoding the production of cytotoxin-associated protein was demonstrated in Hp strains isolated from the patients in 51.3% of cases.

Among 60 siblings of the observed patients, positive results of urea breath test indicating the presence of the bacteria in the stomach were obtained in 38, which accounts for 63.3% of the studied group. The infection occurred more frequently in boys (21/30) than in girls (14/30), but the difference did not reach statistical significance ($p=0.35$).

Incidence of the infection was not dependent on the children's age: in the group below 7 years of age it occurred in 75% of cases, among 7–15-year-olds in 55.5%, and among children over 15 of age in 66.7% (Figure 1).

The incidence was also independent of living conditions, number of siblings, parent's education level, results of urea breath test in mothers. H. pylori infection was diagnosed significantly less frequently in children whose fathers were not infected (37.5%), in comparison with the group of children of Hp-infected fathers (72.7%) – $p=0.027$ (Figure 2).

Dyspeptic symptoms (abdominal pain, nausea, heartburn, vomiting episodes) were reported by 14 children, i.e. 23% of the studied group. In 12 of them (85.7%), Hp infection was confirmed. Dyspeptic symptoms were significantly more frequent among older children over 10 years of age (31.7%) than in those below 10 (5.3%). - $p=0.024$ (Figure 3).

Dyspeptic symptoms occurred more frequently in the families where cagA+ Hp strain was isolated from the infected child, but the differences did not reach statistical significance ($p=0.44$) (Figure 4)

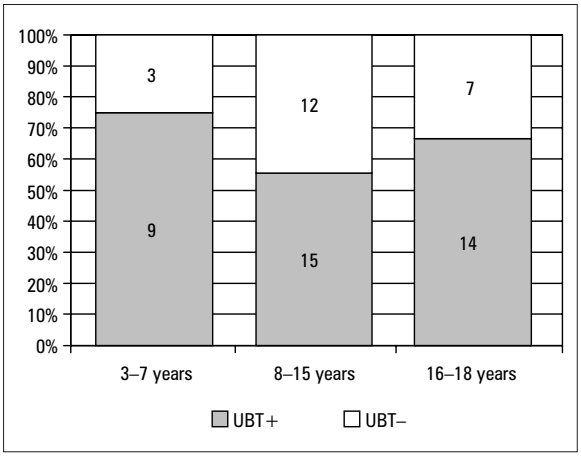

Figure 1. Incidence of Hp infections according to age groups.

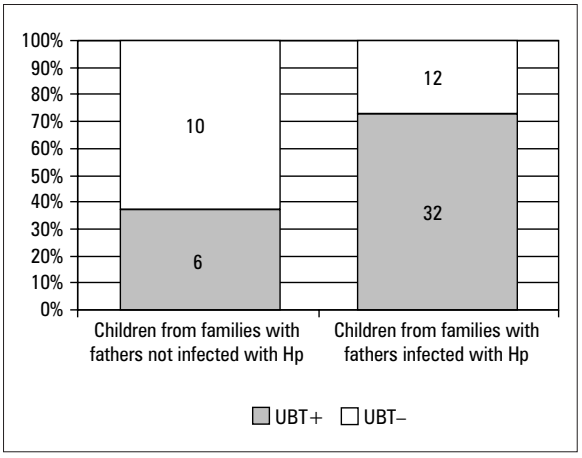

Figure 2. Incidence of Hp infections according to the results of UBT in fathers.

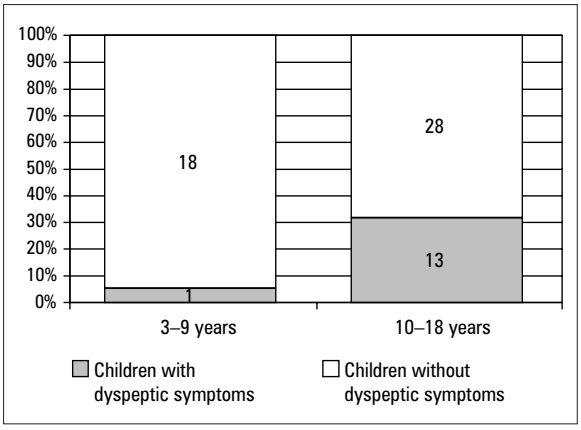

Figure 3. Incidence of dyspeptic symptoms according to age groups.

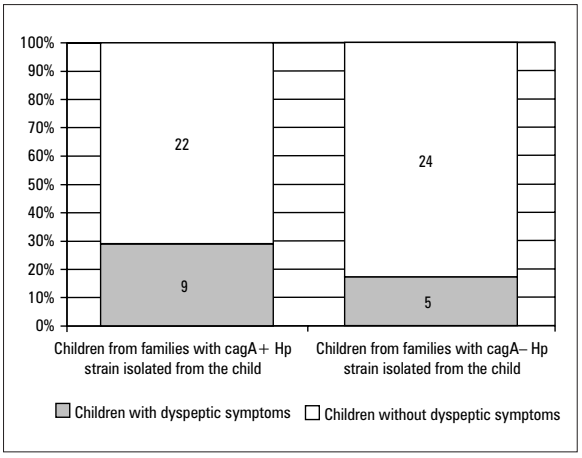

Figure. 4 Incidence of dyspeptic symptoms in siblings depending on the Hp strain type isolated from the infected child.

DISCUSSION

In order to assess the frequency of Hp infection among the siblings of children infected with this pathogen, **^{13}C-urea breath tests** were performed. Most epidemiological studies utilize serological methods to assess the incidence of Hp infection. Determination of IgG anti-Hp antigen antibodies allows to demonstrate contact of the organism with the bacteria. Serological tests provide no information concerning the current status of the infection, because antibodies are present in the serum even over ten months after spontaneous eradication or effective eradication treatment. The annual spontaneous eradication rate is estimated at ca. 2% level [24], but Muszyński in a study of almost 200 inhabitants of Warsaw obtained a spontaneous Hp elimination level of 7.5% [25]. Additionally, in some children and adults with impaired immunity no antibodies may be produced as a result of infection, thus yielding false negative serological test results [26]. Low costs and high availability of the technique are undoubted advantages of serological tests. In the presented study, urea breath test was used to detect Hp in siblings of the children treated for the infection. The choice of this method was determined by its advantages. Urea breath test is a specific, highly sensitive method, providing information about the current status of the infection. It is also noninvasive. The above factor is very important in pediatrics, as well as in epidemiological studies, because it makes it possible to examine many subjects, also those unwilling to consent to invasive procedures such as endoscopy because of lack of any suspicious symptoms. However, the determinations require very expensive, specialist laboratory equipment, but the methodology makes it possible to send the collected material to the laboratory within a few weeks with no influence on the quality of results [2,26–28]. Owing to the method developed by Prof. S. J. Konturek and dr W. Bielański, which was used in the reported study, the costs of testing were also reduced, which is important for epidemiological studies carried out on large populations.

In Polish medical literature, the incidence of Hp infections in our country is estimated at 62–73% [25,29,30]. Epidemiological studies concerning the incidence of Hp infections among children are scarce. The authors most frequently analyze populations of children with dyspeptic symptoms. The occurrence of Hp infections in this group amounts to 30–40%, although in the group of teenagers it reaches 50% [13–16]. Only the studies by

Czkwianianc et al. [17], Bielański at al. [31] and Przybyszewska et al. [18] concerned children without such symptoms. The results obtained by these authors were similar, demonstrating the presence of Hp in ca. 25% of pre-school children, 30% of children below 10 years of age and 45% of teenagers.

Among 60 siblings of the observed patients, positive results of urea breath test indicating the presence of the bacteria in the stomach were obtained in 38, i.e. 63.3% of the studied group, which is considerably more than in the publications concerning the population of healthy children and adolescents cited above. Additionally, high level of infections, exceeding 50%, was observed even among the youngest siblings of pre-school age. These data indicate a significantly higher risk of infection among the siblings of Hp-infected children. This is consistent with the study by Goodman et al. [20], who demonstrated in a large group of children coming from numerous families in Peru that the infection is contracted significantly more frequently by children who have infected siblings, especially older, but with small age difference. Also Drumm et al. [21] demonstrated high (82%) infection rate among the siblings of Hp-infected children. Only the publication by Sedláãkova at al. demonstrates infections in 37% of siblings only [22]. It may be due, besides environmental differences, also to irreliability of the serological method used in the population of children [26].

In the studied population, the incidence of Hp was independent of living standards and the level of parents' education, which is due to small number of examined subjects in comparison with other epidemiological studies, as well as to similar socioeconomic status of the studied families.

Dyspeptic symptoms (abdominal pain, nausea, heartburn, vomiting episodes) were reported by 14 children, i.e. 23% of the studied group. In 12 of them (85.7%), Hp infection was confirmed. Dyspeptic symptoms were significantly more frequent among older children over 10 years of age (31.7%) than in those below 10 (5.3%). Such results may indicate that the presence of Hp is not equivalent with the presence of pathologic symptoms. Higher incidence of dyspeptic symptoms in children over 10 may be due to longer duration of the infection, incorrect diet of older, more self-sufficient children or school-related stress.

Higher toxicity of Hp infection strains possessing the cagA gene is generally accepted [15,32,33]. In the presented study, it was attempted to determine whether the Hp strain type isolated from the patient correlated with the frequency of dyspeptic symptoms in siblings. More children, i.e. 9 out of 14 ones with dyspeptic symptoms, came from the families where cagA+ Hp strain was isolated from siblings. The differences did not reach statistical significance. They might have been more pronounced in a study of a larger population.

High prevalence of Hp among siblings of the children infected with this pathogen makes it necessary to answer the question whether tests detecting the infection should be performed and treatment instituted in the next of kin. This is an important problem if we take into consideration the possibility of reinfection, especially in case of infections with cagA+ Hp strain. Rowland et al. [23] have demonstrated that despite high prevalence of the infection in families (80%), reinfections in children are infrequent. In children over 5 years of age, they approximate 2% a year, regardless of socioeconomic status. In own material [34], reinfections were observed in 5 of 29 children subjected to urea breath test over a year after the completion of treatment (17%). Considering the fact that the effectiveness of treatment reaches 70–90% in the population of children, the incidence of reinfections is probably low, comparable to Rowland's observations. In view of these facts, it would seem feasible to examine family members and possibly institute treatment in cases of reinfections after previous effective eradication. Such approach seems especially justifiable in patients with peptic ulcer disease and those infected with cagA+ Hp strain, regarded as more pathogenic. This is also supported by economic considerations. Ultimate determination of Hp transmission routes may allow to assess more precisely the risk of contracting the infection by children in the families whose members are carriers of this microorganism.

CONCLUSIONS

1. The incidence of *Helicobacter pylori* (Hp) infections in siblings of children with gastritis and/or duodenitis coincident with Hp infection is high.

2. High incidence of infections is observed even among the youngest children (3–7 years), but they are usually not accompanied by dyspeptic symptoms.

3. Dyspeptic symptoms, which may indicate peptic ulcer disease or gastritis in siblings of Hp-infected children are frequent and exacerbate over 10 years of age (at school age).

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